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Antagonism of the intracellular action of botulinum neurotoxin type A with monoclonal antibodies that map to light-chain epitopes.

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mAbs were produced in mice against highly purified, renatured light chain (LC) of botulinum neurotoxin A (BoNT A) that was immobilised on nitrocellulose to avoid the undesirable use of toxoids. Subcutaneous implants of relatively high amounts (up to 10 micrograms each) of LC allowed its slow release into the systemic circulation and, thus, yielded much higher antibody titres against the underivatized antigen than had hitherto been obtained by conventional immunization. Seven stable hybridoma cell lines were established which secrete mAb of IgG1 and IgG2b subclasses reactive specifically with BoNT A and LC, in native and denatured states, without showing any cross-reactivity with types B, E, F or tetanus toxin. The pronounced reactivities of three mAbs towards refolded LC or intact toxin, observed in immunobinding and precipitation assays, relative to that seen in Western blots imply a preference for conformational epitopes. Though mAbs 4, 5 and 7 failed to neutralize the lethality of BoNT in vivo, administration intraneurally of mAb7 prevented the inhibition of transmitter release normally induced by subsequent extracellular administration of BoNT A. Notably, the latter mAb reacted with a synthetic peptide corresponding to amino acids 28-53 in the N-terminus of the LC, a highly conserved region in Clostridial neurotoxins reported to be essential for maintaining the tertiary structure of the chain. Most importantly, when mAbs 4 or 7 were microinjected inside ganglionic neurons of Aplysia, each reversed, though transiently, the blockade of acetylcholine release by the toxin; this novel finding is discussed in relation to the nature of the zinc-dependent protease activity of the toxin.

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Identification and characterization of a neutralizing monoclonal antibody against botulinum neurotoxin serotype F, following vaccination with active toxin.

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Clostridium botulinum may produce any of seven known serotypes of neurotoxin (BoNT/A-/G), which are the most toxic bacterial proteins known. Efforts to develop a second-generation vaccine to these toxins would benefit from the isolation of hybridomas producing neutralizing monoclonal antibodies (MAbs). We hypothesized that previous efforts to isolate neutralizing MAbs against various BoNTs failed due to use of toxoided, chemically altered antigens. We employed a novel vaccination regimen employing native, active, single-chain BoNT/E (scBoNT/E). A number of the BoNT/E immunized mice were further vaccinated with lethal doses of fully active BoNT/F. MAb 7F8 consistently neutralized BoNT/F in three different assays: in vivo neutralization, passive neutralization, and neutralization of regional paralysis. There was no detectable recognition and essentially no neutralization of scBoNT/E. The epitope recognized by this MAb was denatured when treated with formalin, urea, guanidine chloride, or sodium dodecyl sulfate. Preliminary epitope mapping studies indicate that the MAb bound to a conformational epitope.

PMID: 9388028 [PubMed - indexed for MEDLINE]